Physician Messaging and Brochure Content

Epi proColon®

The Blood Test for Colorectal Cancer Screening

Epi proColon is an approved blood test for colorectal cancer screening. The US Preventive Services Task Force, the American Cancer Society and other medical groups recommend colorectal cancer screening for women and men beginning at the age of 50. There are a number of screening tests to choose from including colonoscopy and fecal blood tests. The Epi proColon test provides an additional option to consider for colorectal cancer screening.

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The Epi proColon Test Intended Use

The Epi proColon test is a qualitative *in vitro* diagnostic test for the detection of methylated Septin9 DNA in EDTA plasma derived from patient whole blood specimens. Methylation of the target DNA sequence in the promoter region of the *SEPT*9_v2 transcript has been associated with the occurrence of colorectal cancer (CRC).[1] The test uses a real-time polymerase chain reaction (PCR) with a fluorescent hydrolysis probe for the methylation specific detection of the Septin9 DNA target.

The test is indicated to screen patients for colorectal cancer who are defined as average risk for colorectal cancer (CRC) by current CRC screening guidelines. Patients with a positive Epi proColon test result should be referred for diagnostic colonoscopy. Men and women 50 to 85 years of age were included in the Epi proColon clinical trial. The Epi proColon test results, together with the physician's assessment of history, other risk factors, and professional guidelines, may be used to guide patient management.

The Epi proColon test is for use with the Applied Biosystems 7500 Fast Dx Real-Time PCR Instrument.

Warnings

- The Epi proColon test is not intended to replace colorectal screening by colonoscopy.
- The Epi proColon test is not intended to screen persons under the age 50 who are considered to be at average risk for colorectal cancer.
- Positive Epi proColon test results are not confirmatory evidence for the presence of colorectal cancer. Patients with a positive Epi proColon test result should be referred for diagnostic colonoscopy.
- A negative Epi proColon test result does not guarantee absence of cancer. Patients with a negative Epi proColon test result should be advised to continue participating in a colorectal cancer screening program that also includes colonoscopy, fecal tests and/or other recommended screening methods.
- Positive test results have been observed in clinically diagnosed patients with chronic gastritis, lung cancer and in pregnant women. [5,11]

Note: The Epi proColon test has not been tested in persons considered to be at higher-risk for colorectal cancer.

About CRC and Screening

- Anyone can get CRC—CRC affects women and men, and all races and ethnicities
- 1 in 3 people still choose not to be screened by any method in the US[1]
- 9 out of 10 people will survive when CRC is detected early—today, less than half of persons with CRC are diagnosed in the early stages of disease[2]
- About 9 out of 10 people choose not to complete fecal blood tests[2]
- Inconvenience, discomfort, and fear, among other barriers, contribute to non-participation[2]

Who Should Be Screened?

Professional colorectal cancer screening guidelines recommend the following and emphasize its importance in both preventing colorectal cancer and finding cancer early at a stage where cure is still possible.

AVERAGE-RISK PERSONS: Women and men 50 years of age and older with no personal history of polyps, previous CRC, inflammatory bowel disease or family history of CRC are considered average-risk for developing colorectal cancer and should be screened.[1,2]

The United States Preventive Services Task Force (USPSTF) also recommends that the screening of women and men between the ages 75 and 85 be based on a discussion with their healthcare provider; however, screening is not recommended for persons over the age of 85.[3]

HIGHER-RISK PERSONS: Persons at higher-risk for developing CRC include those with a family history of CRC, particularly two or more first-degree relatives with CRC or one or more first degree relative(s) less than 50 years of age with CRC, personal or family history of benign polyps in the colon or rectum, Crohn's disease, inflammatory bowel disease, genetic syndromes like Lynch syndrome (hereditary non-polyposis colorectal cancer) or FAP (familial adenomatous polyposis) and other lifestyle factors.[1,2]

Based on your patient's individual health history, a screening plan that also includes colonoscopy, fecal tests, and/or other recommended screening methods scheduled at more frequent intervals, should be considered for patients considered to be at higher-risk for CRC.[2]

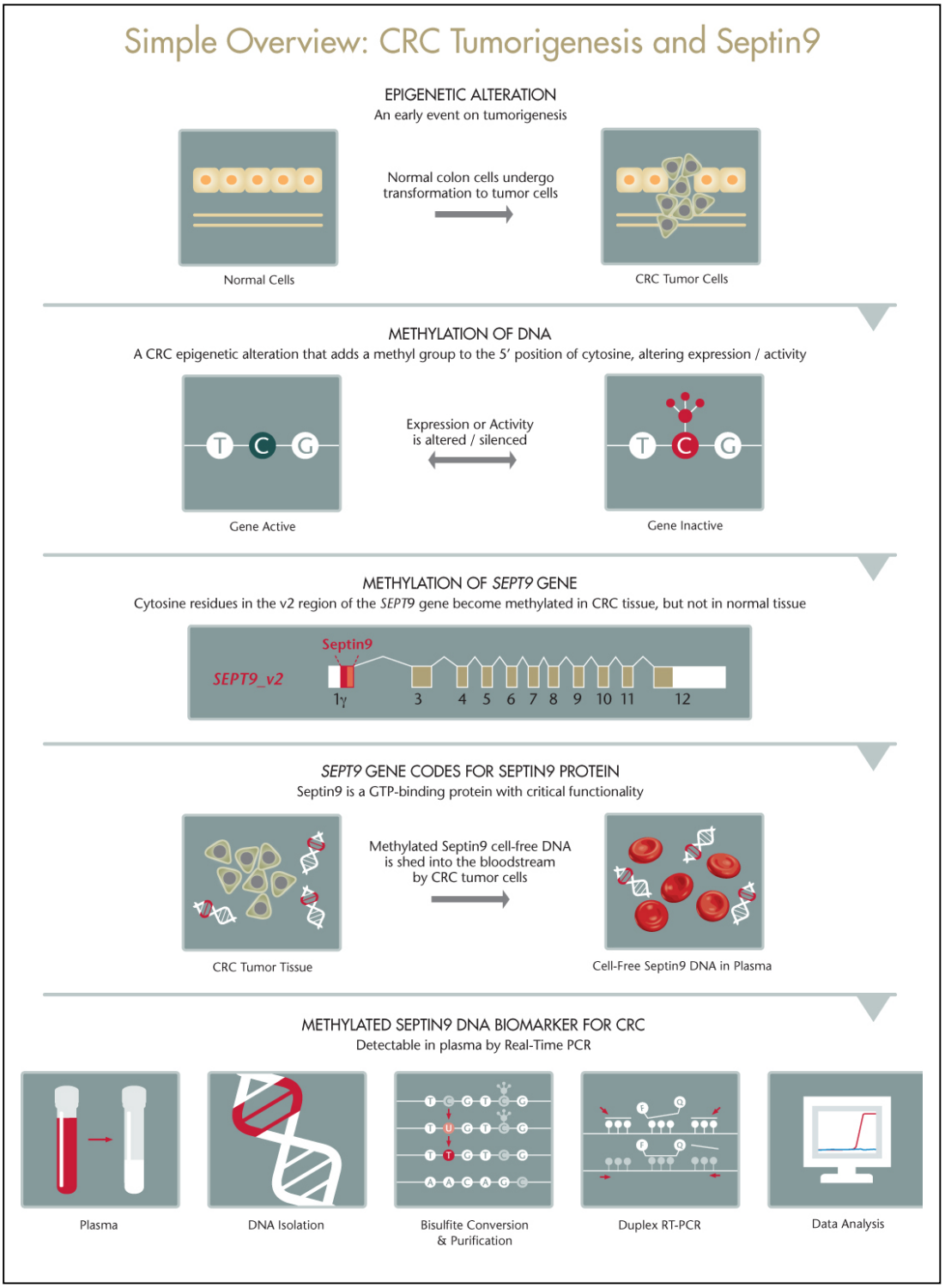
Note: Epi proColon has not been validated for persons considered to be at higher-risk.

Epi proColon, the Septin9 DNA Biomarker, and CRC

- Epi proColon is a molecular DNA test that detects methylated Septin9 DNA in blood.[4]
- Septin9 DNA is specifically hypermethylated in colorectal cancer, but not in normal colon or rectal tissue. This unique methylation pattern is detectable by Real-Time PCR.[4]
- Hypermethylated Septin9 DNA can be found in tumor DNA that has been shed into the bloodstream from all intestinal anatomical sites (proximal and distal colon, rectum), making it a differential blood biomarker for the early detection of colorectal cancer.[4]

Note: The Epi proColon test is indicated to screen patients defined as average risk for colorectal cancer by current screening guidelines. Men and women 50 to 85 years of age were included in the clinical evaluation. The Epi proColon test results, together with the physician's assessment of history, other risk factors, and professional guidelines may be used to guide patient management.

Figure 1: Simple Overview: CRC Tumorigenesis and Septin9 (Ready Reference 2012: Vol. 2)



Patient Testing

Your patient's blood sample may be drawn in your office laboratory or other local or US clinical laboratories as designated by your patient's healthcare plan.

- The test does not require pretest dietary or medication restrictions before blood is drawn.
- Your patient's test might take a few days to be completed.
- Share the Epi proColon test results with your patient, and together, decide if there is any additional follow-up necessary.
- Patients with positive Epi proColon test results should be referred for diagnostic colonoscopy.

Note: This product has been validated ONLY with the Vacutainer® K_2EDTA Blood Collection Tube. See Precautions, Contraindications and Warnings in this brochure; refer to the Epi proColon Instructions for Use (IFU) for more information on results interpretation.

Benefits of Screening with Epi proColon

- When CRC is detected early, cure is still possible. A good prognosis is directly related to early detection and the timing of diagnosis.[2]
- Epi proColon detects methylated Septin9 DNA that is highly associated with colorectal cancer.
- A blood test is a common, minimally invasive, accepted method of testing.[6-9]
- If your patient is unwilling or unable to be screened for CRC by colonoscopy or other recommended methods, the Epi proColon blood test is another test choice to consider for CRC screening.[9,10]

Note: Epi proColon is not intended to replace colorectal cancer screening by colonoscopy.

Clinical Summary

In a large, prospective multicenter clinical trial, 7,941 women and men, ages 50 to 85, who are of average-risk for colorectal cancer were enrolled at 32 clinical sites in the US and Germany.[5] The Epi proColon test's clinical performance has been validated in 1,544 of the trial participants, using colonoscopy as the reference standard. The study included all patients with colorectal cancer (all stages) or advanced adenomas, a subset of patients with small polyps, and patients with no evidence of disease (NED), Tables 1 and 2.

Table 1: Epi proColon Clinical Trial Results for Different Patient Groups: Specificity = 70% (1182/1500)

Classification	Positives (Total)
NED (No Evidence of Disease)	97 (444)
Polyps	87 (435)
Advanced Adenomas	134 (621)

Table 2: Epi proColon Clinical Trial Results for Colorectal Cancer (CRC) Stages: Sensitivity = 68% (30/44)

CRC Stage	Positives (Total)	Percent Positive
Stage I	7 (17)	41%
Stage II	10 (12)	83%
Stage III	8 (10)	80%
Stage IV	5 (5)	100%
Total Cancers	30 (44)	68%

In a second, large multicenter clinical trial, the Epi proColon test was compared to a widely-used US commercial fecal immunochemical test (FIT). The study was designed to collect matched blood and fecal specimens and clinical data from screening guideline-eligible subjects using colonoscopy as the reference method for detection of CRC.

Subjects were recruited at 61 clinical sites in the US according to the following scheme:

- Subjects having CRC or a high suspicion of invasive CRC identified during screening colonoscopy were enrolled and provided blood and fecal samples at least 10 days after colonoscopy but prior to surgery or intervention
- Prospectively enrolled subjects provided blood and fecal samples prior to bowel prep for screening colonoscopy

Of 337 subjects enrolled in the study, 36 were excluded due to failure to meet inclusion/exclusion criteria. From the remaining 301 enrolled subjects, there were 101 patients with colorectal cancer (CRC), 29 with advanced adenomas (AA), 77 with small polyps (SP) and 94 with no evidence of disease (NED). Plasma samples were available from all 301 subjects. Fecal samples were not available from 11 subjects (4 CRC, 2 AA, 2 SP and 3 NED).

Results from the Epi proColon and FIT tests were compared to results obtained with colonoscopy, as shown in Table 3. Tables 4 - 6 present sensitivity and specificity results for the Epi proColon test and the FIT test.

Table 3. Three – way comparison of Epi proColon, FIT and Colonoscopy results.

Diagnostic Accuracy Criteria: Standard Colonoscopy						
	Colorectal Cancer			Non-Colorectal Cancer AA, SP, NED		
	Epi proColon Positive	Epi proColon Negative	Total	Epi proColon Positive	Epi proColon Negative	Total
FIT Positive	50	16	66	1	4	5
FIT Negative	20	11	31	36	152	188
Total	70	27	97	37	156	193

Table 4: Epi proColon Sensitivity and Specificity for all samples (n=301)

	Epi proColon Test	95% CI	
Sensitivity	73.3% (74/101)	63.9%	80.9%
Specificity	81.5% (163/200)	75.5%	86.3%

Table 5: Epi proColon Sensitivity and Specificity for paired samples (n=290)

	Epi proColon Test	95% CI	
Sensitivity	72.2% (70/97)	62.5%	80.1%
Specificity	80.8% (156/193)	74.7%	85.8%

Table 6: OC FIT-CHECK Sensitivity and Specificity for paired samples (n=290)

	FIT Test	95% CI	
Sensitivity	68.0% (66/97)	58.2%	76.5%
Specificity	97.4% (188/193)	94.1%	98.9%

The observed sensitivity for CRC on paired samples was 4.2% higher for the Epi proColon test (Table 5 & 6). The sensitivity of the Epi proColon test is statistically non-inferior to the FIT test.

For specificity, the difference between tests was 16.6% in favor of the FIT (Table 5 & 6). This result does not demonstrate non-inferiority for specificity.

Understanding Epi proColon Test Results

- A **POSITIVE BLOOD TEST RESULT** indicates that methylated Septin9 DNA has been detected in the plasma sample tested. Methylated Septin9 DNA has been associated with the occurrence of colorectal cancer[4]. Because the Epi proColon test is not a confirmatory test for the presence of colorectal cancer, patients with positive Epi proColon test results should be referred for diagnostic colonoscopy.

  Note: Positive test results have been observed in clinically diagnosed patients with chronic gastritis, lung cancer and in pregnant women.[5,11] Because a colonoscopy procedure examines the interior lining of the colon and rectum, CRC is unlikely when no abnormal findings are discovered during this procedure.

- A **NEGATIVE BLOOD TEST RESULT** indicates the absence of methylated Septin9 DNA in the plasma sample tested. Because a negative test result is not confirmatory for the absence of colorectal cancer, persons should be advised to continue participating in a colorectal cancer screening program that also includes colonoscopy, fecal tests and/or other recommended screening methods.

  Note: Studies show that methylated Septin9 DNA is not present in plasma from all patients with colorectal cancer and therefore, a negative test result does not guarantee absence of cancer.[5] Detection of CRC is dependent on the amount of circulating tumor DNA in the plasma specimen and may be affected by sample collection methods, sample storage, patient factors and tumor stage.[5]

CPT Code Information

81401, Molecular pathology procedure, Level 2, *SEPT*9 (Septin9)(eg, colon cancer), methylation analysis.

Precautions, Contraindications and Warnings

Precautions

- The Epi proColon test is an alternative screening method for patients who are defined as average-risk for colorectal cancer by current screening guidelines.
- The Epi proColon test was positive 2 out of 10 times when colorectal cancer was not present. The Epi proColon test was negative 3 out 10 times when colorectal cancer was present.
- Detection of colorectal cancer is dependent on the amount of free circulating tumor DNA in the specimen and may be affected by sample collection methods, sample storage, patient factors and tumor stage. Some CRC tumors may not shed methylated Septin9 into the blood.
- There is insufficient evidence to report programmatic screening sensitivity for the Epi proColon test over an established period of time.
- CRC guideline recommendations vary for persons over the age of 75. The decision to screen patients over the age of 75 should be made on an individualized basis through shared decision-making with your patient.
- The Epi proColon test demonstrated non-inferiority to a FIT test (OC FIT-CHEK® Polymedco Inc.), for sensitivity but not for specificity, indicating that the Epi proColon test exhibited a higher rate of false positive results compared to the FIT test.
- The Epi proColon test has been validated for use only with plasma derived from blood collected with BD Vacutainer® blood collection tubes (Becton Dickinson). Do not use this test with other clinical specimen types or with other blood collection tubes.
- As with all screening methods, test results should be interpreted by a healthcare professional.

Contraindications

- The Epi proColon test was not tested in persons considered to be at higher-risk for developing CRC. Persons at higher-risk for developing CRC include those with a family history of CRC, particularly two or more first degree relatives with CRC or one or more first degree relative(s) less than 50 years of age with CRC, personal or family history of benign polyps in the colon or rectum, Crohn's disease, inflammatory bowel disease, genetic syndromes like Lynch syndrome (hereditary non-polyposis colorectal cancer) or FAP (familial adenomatous polyposis) and other lifestyle factors.
- This test was also not evaluated in persons with anorectal bleeding, hematochezia or with known iron deficiency anemia.
- For persons considered to be at higher risk for colorectal cancer, a screening and management plan that also includes colonoscopy should be considered.[2]
- For patients diagnosed and treated for colorectal cancer, a disease monitoring and management plan should be discussed with your patient based on their individual health history.[2]

- If your patient has signs and symptoms of colorectal cancer, a diagnostic colonoscopy is recommended.[2]

Warnings

- The Epi proColon test is not intended to replace colorectal screening by colonoscopy.
- The Epi proColon test is not intended to screen persons under the age 50 who are considered to be at average risk for colorectal cancer.
- Positive Epi proColon test results are not confirmatory evidence for the presence of colorectal cancer. Patients with a positive Epi proColon test result should be referred for diagnostic colonoscopy.
- A negative Epi proColon test result does not guarantee absence of cancer. Patients with a negative Epi proColon test result should be advised to continue participating in a colorectal cancer screening program that also includes colonoscopy, fecal tests and/or other recommended screening methods.
- Positive test results have been observed in clinically diagnosed patients with chronic gastritis, lung cancer and in pregnant women.[5,11]

References and Resources

1. Centers for Disease Control. "Vital Signs: Colorectal cancer screening, incidence, and mortality—United States, 2002-2010." MMWR Morb. Mortal. Weekly Report. 2011. 60(26):884-889
2. American Cancer Society. Colorectal Cancer Facts and Figures, 2011-2013.
3. United States Preventive Task Force Services (USPSTF), American Cancer Society (ACS) and American College of Gastroenterology (ACG) Guideline Recommendations, Dec 2010 and 2013.
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5. Epi proColon Instructions for Use (IFU) and Epigenomics data on file.
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7. Adler A et al. Improving compliance to CRC screening by blood and stool-based tests in patients refusing colonoscopy in Germany. UEGW, Oct, 2012.
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9. Inadomi J et al. Adherence to colorectal cancer screening, a randomized clinical trial of competing strategies. Arch Intern Med. 2012, (172(7):575-582.
10. Levin T. The importance of choosing colorectal cancer screening tests. Invited commentary. Arch Intern Med. 2012, (172(7):582-583.
11. Warren, D. et al. Septin 9 methylated DNA is a sensitive and specific blood test for colorectal cancer. BMC Med. 2011, (9)133.

CRC Resources	Web Address
American Cancer Society	www.cancer.org
American College of Physicians	www.acponline.org
American College of Gastroenterology	www.gi.org
American Gastroenterology Association	www.gastro.org
Centers for Disease Control	www.CDC.gov/vitalsigns
Colorectal Cancer Alliance	www.cca.org
Fight Colorectal Cancer	www.fightCRC.org
National Cancer Institute	www.cancer.gov/cancertopics/factsheet/detection/colorectal-screening
US Preventive Services Task Force	www.ahrq.gov/clinic/uspstfix.htm

For More Information

Please visit our website at EpigenomicsUSA.com, and select the "Q & A" tab where you will find many answers to commonly asked questions about the Epi proColon Test. For a list of US Laboratories that offer the Epi proColon test, please refer to the website. To learn more about the Company and our products, please visit our website, EpigenomicsUSA.com, or contact us in any of the other following ways:

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